UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

Clarksburg

ACTELION PHARMACEUTICALS LTD,	)	Civil Action No. 1:20-110 (JPB)
	)	
Plaintiff,	)	Hon. John Preston Bailey
	)	
v.	)	**ACTELION'S BRIEF REGARDING**
	)	**EXTRINSIC EVIDENCE**
MYLAN PHARMACEUTICALS INC.,	)	**SUPPORTING THE COURT'S**
	)	**CLAIM CONSTRUCTION**
Defendant.	)	
	)	
	)	

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I. INTRODUCTION

U.S. Patent Nos. 8,318,802 and 8,598,227 ("the patents-in-suit") protect Actelion's Veletri® (epoprostenol). Veletri® treats pulmonary arterial hypertension ("PAH"). PAH is a progressive disease that ultimately results in heart failure. Veletri® represented a new, stable formulation of epoprostenol that allows more patients to self-administer their medication, preserving their personal independence through the course of PAH.

The claims cover a composition comprising epoprostenol, arginine, and sodium hydroxide. The disputed limitation recites that this composition is "formed from a bulk solution having a pH of 13 or higher." A pH of 13 is a highly basic[1] composition, which was expected to be harmful to patients by destroying blood cells. However, the design was extraordinary. It surprisingly achieved the desired high stability without adverse effects on patients. '802 patent at 4:38-47.[2]

Actelion has maintained the same claim construction position throughout this litigation: The claim language "pH of 13" means the whole number of 13 on the pH scale, subject to ordinary numerical rounding (12.5 to 13.4). In support of this construction, Actelion cited extrinsic evidence during the claim construction proceedings.

Mylan has presented at least three different claim construction positions. First, before Judge Keeley, Mylan primarily argued that "the '802 Patent uses the numeral 13 to mean 13.0." Mylan Opening Claim Construction Br. (Dkt. 62) at 12. Second, in its opening Federal Circuit

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[1] Acidic compounds (pH 0-6) have an excess of hydrogen ions in comparison to the neutral baseline comparator used in chemistry – purified water. Purified water has a pH of 7. Basic compounds (pH 8-14) have fewer hydrogen ions than baseline purified water. The presence of excess hydrogen ions in acids causes compounds that come in contact with the acid to "dissolve," which is to say, chemical bonds are broken by the hydrogen ions. Stomach acid has a low pH 2, and is therefore extremely acidic. It is for this reason that a folk remedy for acid reflux is to drink water mixed with baking soda. Baking soda is a basic compound, with a pH of 9.

[2] The '802 and '227 patents share a common parent application and have the same specification.

brief, Mylan instead primarily argued that "'13' here means a pH of *exactly* 13." Ex. 9, Mylan Opening App. Br. at 1. Third, in its reply appellate brief, Mylan alternatively argued that "13" means a range of "12.995-13.004." Ex. 10, Mylan App. Reply Br. at 12. Except for a glancing discussion of pictures of pH meters (which Mylan misinterprets), Mylan avoided engaging the extrinsic record, urging that the textbooks cited by Actelion be ignored. This was not an accident.

The extrinsic evidence confirms Actelion's construction, and refutes each of Mylan's responsive arguments. The extrinsic evidence establishes that when pH is recited as a whole number (here, 13), it refers to an order of magnitude of hydrogen ion concentration (here, 10^{-13}). This is explained in the following table, "Understanding pH," from a textbook that Actelion submitted, and the Federal Circuit identified as pertinent extrinsic evidence.

Table 10.7 Understanding pH

Range of acidity and basicity	$[H_3O^+]$ (mol/L)	Exponential notation (mol/L)	log	pH ($-\log [H_3O^+]$)
strong acid	1	1×10^{0}	0	0
	0.1	1×10^{-1}	−1	1
	0.01	1×10^{-2}	−2	2
	0.001	1×10^{-3}	−3	3
	0.000 1	1×10^{-4}	−4	4
	0.000 01	1×10^{-5}	−5	5
	0.000 001	1×10^{-6}	−6	6
neutral $[H^+] = [OH^-] = 1.0 \times 10^{-7}$	0.000 000 1	1×10^{-7}	−7	7
	0.000 000 01	1×10^{-8}	−8	8
	0.000 000 001	1×10^{-9}	−9	9
	0.000 000 000 1	1×10^{-10}	−10	10
	0.000 000 000 01	1×10^{-11}	−11	11
	0.000 000 000 001	1×10^{-12}	−12	12
	0.000 000 000 000 1	1×10^{-13}	−13	13
strong base	0.000 000 000 000 01	1×10^{-14}	−14	14

Hydrogen ion concentration

pH whole number scale

Ex. 1, Frank Mustoe et al., CHEMISTRY 11, at 386 (2001) ("Mustoe") (blue annotations added).

The pH scale represents a relative concentration of hydrogen ions in a solution (the more hydrogen ions, the more acidic the solution is). As another textbook submitted by Actelion and referenced by the Federal Circuit teaches, the number of hydrogen ions in a solution is vast and not countable.[3] Thus, the textbooks explain that the pH scale was designed "as a simple system" "without units."[4] Instead of precisely counting the ions, indirect analysis is performed, for example using an electrical current and sensor. The pH scale can translate the results into scaled whole number values such as those shown above (e.g., "pH of 13," corresponding to the order of magnitude 10^{-13}). As the textbooks presented by Actelion and commended by the Federal Circuit make clear, "[t]here are several different ways of measuring the pH of a solution, some more precise than others." Ex. 2, Kessel at 543. The extrinsic evidence thus directly refutes Mylan's argument to the Federal Circuit that "pH of 13" should be construed as "exactly 13." pH—by both design and necessity—is not an "exact" unit of measure. In fact, as those textbooks describe, the pH scale is "without units."

The textbooks Actelion presented establish that the historical pH scale has 15 single-digit steps: pH 0, pH 1, pH 2 . . . pH 6 . . . pH 12, pH 13, pH 14. In math, these are referred to as whole numbers, because there are no decimals. The patents' claims track this scale, reciting a whole number, "pH of 13," without any decimals. The claims do not recite pH of 13.0 or 13.00. A person of skill recognizes as significant only the digits actually stated. Ex. 1, Mustoe at 387 ("How do

[3] Ex. 2, Hans van Kessel et al., CHEMISTRY 12, at 540 (2003) ("Kessel") ("Because of the tremendous range of hydrogen ion and hydroxide ion concentrations, scientists rely on a simple system for communicating concentrations. This system, called the pH scale, was developed in 1909 by Danish chemist Soren Sorenson. Expressed as a numerical value without units, the pH of a solution is the negative of the logarithm to the base ten of the hydrogen ion concentration.").

[4] *Id.*

you determine the number of significant digits in a pH? You count only the digits to the right of the decimal point."). Because the claim language "pH of 13" does not state digits to the right of a decimal point, no additional significant digits are read into the claims. The only significant digits present in the claim are the two digits in the whole number "13" itself, and conventional whole number rounding standards apply. Values between 12.5 and 13.4 round to the whole number 13.[5]

Moreover, as explained above and in Mustoe's table "Understanding pH," a pH of 13 corresponds to an "exponential" (10^{-13}). Standard textbooks explain that exponentials used to communicate orders of magnitude are rounded as well, giving the example that, for $10^{3.633}$, "the order of magnitude is 10^{4}." Ex. 3, Kerr at 2. Consistent with the Kerr textbook, a person of skill understands that reported pH values from 12.5-13.4 (corresponding to $10^{-12.5} – 10^{-13.4}$) slot into the whole number score of pH 13 (corresponding to 10^{-13}).

Looking beyond the texts specifically identified by the Federal Circuit, additional extrinsic evidence further confirms that Judge Keeley's construction is correct. As discussed above, there are many ways to report pH, some using whole numbers and others one or two decimal places. The claims use the whole number approach, "pH of 13," as opposed to a higher level of granularity. This makes particular sense in the context of the invention because, in the preferred embodiment, the solution is created by "adjusting the pH of the bulk solution" by adding "sodium hydroxide," a very strong base. '802 patent at 5:23–30, 35–43. At the time of the invention, commercial data

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[5] Mylan does not dispute that the whole number 13 has two significant figures, *see, e.g.*, Mylan Responsive Claim Construction Brief (Dkt. 75) at 13. Under ordinary mathematics standards, this means it is rounded to the last reportable digit (here, the "3"). Ex. 3, GREGG KERR & PAUL RUTH, PHYSICS, Chapter 1, at 8–9 (3d ed. 2008) ("Kerr").

sheets show sodium hydroxide sold as simply "pH 13" or "pH 13-14,"[6] similarly using the broader whole number scale of magnitude, rather than a value reported to decimal units.

The Federal Circuit instructed that "the district court should consider whether a pH of 13 carries any meaning to a person of ordinary skill in the art as regards precision of measurement, significant digits, or rounding," specifically including "understanding what the significant digits are for 'a pH of 13.'" *Actelion Pharms. Ltd v. Mylan Pharms. Inc.*, No. 2022-1889, slip op. at 9, 2 (Fed. Cir. Nov. 6, 2023). As discussed herein, the extrinsic evidence leads inescapably to Actelion's and Judge Keeley's construction. The only significant digits in claim language of "pH of 13" are the digits actually recited in the claim language, the ones and tens place. Thus, the claims recite the whole number of 13 on the pH scale, and are subject to ordinary numerical rounding (12.5 to 13.4). Mylan admitted as much in its appellate briefing, where it vigorously argued against consideration of the very Actelion extrinsic evidence that the Federal Circuit has now directed must be addressed. Ex. 10, Mylan App. Reply Br. at 6 ("That is precisely what Actelion is trying to do in this case…defining a claim term using textbooks"), 32 ("[Actelion's] proposed construction, based from the beginning on extrinsic evidence").

Pursuant to the Federal Circuit's remand order, Actelion respectfully requests that the Court make the factual determinations set forth herein, and reaffirm that "a pH of 13" carries its plain and ordinary meaning of pH 13, subject to standard rounding principles for whole numbers (*i.e.*, 12.5 to 13.4 rounds to 13). In this brief, the term "whole number" or "whole number measure" will refer to this this plain and ordinary meaning of pH 13.

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[6] *See, e.g.*, Ex. 6, Philip A. Hunt Chemical Corporation, *Sodium Hydroxide Caustic Soda 30%*, at 1 (1996) (pH 13); Ex. 5, TETRA Technologies, Inc., *Caustic Soda*, at 3 (2001) (pH 13); Ex. 7, Fischer Scientific, *Sodium Hydroxide 1N*, at 4 (2005) (pH 13-14).

II. PROCEDURAL HISTORY

During the claim construction proceedings in the district court, the "central conflict" presented by the parties was "the weight given to the integers used to express 'a pH of 13 or higher,' *i.e.*, 13 or 13.0, in the patent specification." Dkt. 143 at 13. Mylan argued that "13" should be re-written as "13.0." *See* Mylan Opening Claim Construction Br. (Dkt. 62) at 17 ("the '802 Patent uses the numeral 13 to mean 13.0"), 18 ("Here, '13' must mean '13.0.'"), *id.* ("'13' represents the more precise value '13.0.'").

Judge Keeley rejected Mylan's argument, observing: "In the claims at issue, Actelion consistently expressed 'a pH of 13' … This claim language provides no basis for inferring any higher level of precision. Accordingly, under its conventional significant figure meaning, the term a 'pH of 13' would ordinarily encompass those values that round up or down to 13, 12.5 to 13.4." Dkt. 143 at 13. The district court also discussed the specification. Judge Keeley noted that the specification "expressed pH and, specifically, 'a pH of 13,' with varying degrees of precision. …," but found "nothing to indicate that Actelion intended to import any higher degree of precision to 'a pH of 13' as it is articulated in the claims at issue[.]" *Id.* at 14, 16–17.

On appeal to the Federal Circuit, Mylan shifted position, abandoning its unsuccessful, primary argument in the district court that the claim should be read as 13.0, apparently recognizing that this position contradicts the specification. The specification illustrates that Actelion reported pH to the level of granularity of 13.0 for certain experiments. *See* '802 patent at 9:46–57 ("the pH of the solution containing epoprostenol and arginine was adjusted to 13.0 with sodium hydroxide"). However, Actelion did not claim the specific reported value of 13.0 in the claims, but rather "pH of 13," tracking the "pH of 13 or higher" language of the preferred embodiment, and the data regarding pH 13 that was the focus of most of the comparative data and experiments. *See,*

e.g., *id.* at 5:37 ("most preferably greater than 13"); cols. 12–14 Tbls. 10–18 (providing data for experimental batches with "pH 13"). On appeal, Mylan instead focused largely on an argument that the claims prohibit *any* rounding, and should be construed as "exactly 13." *See, e.g.*, Ex. 9, Mylan Opening App. Br. at 1 ("'13' here means a pH of *exactly* 13"), 30–31 ("'13' in '13 or higher' means *exactly* 13, and does not include values as low as '12.5'") (emphasis in original). Then, in its reply brief, Mylan shifted position again, alternatively arguing to the Federal Circuit that "13" means a range of "12.995-13.004." Ex. 10, Mylan App. Reply Br. at 12; *Actelion Pharms.*, slip op. at 7 ("In the alternative, Mylan argues that if a margin of error for a pH of 13 is needed, a pH of 13 would involve rounding to the hundredths place, encompassing 12.995–13.004.").

Mylan's briefing before the Federal Circuit assiduously avoided engaging the extrinsic record, with the sole exception of the plainly incorrect argument that three images of pH meters reporting pH to the hundredths place somehow limit the claims. *See* Ex. 10, Mylan App. Reply Br. at 11–12. Notably, Mylan repeatedly conceded that Actelion's construction tracks the extrinsic evidence, purporting to criticize Actelion for presenting a construction based on definitions in the very extrinsic evidence that the Federal Circuit has now instructed must be considered. *Id.* at 6 ("That is precisely what Actelion is trying to do in this case…defining a claim term using textbooks"), 32 ("[Actelion's] proposed construction, based from the beginning on extrinsic evidence").

In its remand order, the Federal Circuit identifies each of these texts as pertinent. Specifically, the Federal Circuit agreed with Judge Keeley that the specification uses various degrees of precision, noting: "the specification uses both '13' and '13.0'—and various degrees of precision for pH values generally—throughout." *Actelion Pharms.*, slip op. at 10. However, the

Federal Circuit found that this rendered the intrinsic record sufficiently "equivocal" that it was appropriate to make specific findings from the extrinsic evidence. *Id.* at 7. Specifically, the Federal Circuit noted that the extrinsic evidence presented by Actelion but not specifically discussed in the district court's claim construction order included textbooks affirming that the way to identify "significant digits in a pH" is by counting the number of "digits to the right of the decimal point." *Id.* at 5 (quoting Mustoe at 339[7]). However, the Federal Circuit declined to make any findings based on that evidence, explaining that the district court, as finder of fact, was the proper entity to do so:

> "We decline to decide, for example, how many significant figures 'a pH of 13' has or what it would mean for a number—either for a pH value or for the concentration of hydrogen ions—to have zero significant figures. Instead, we leave those and other relevant factual questions that might arise based on the extrinsic evidence, including the three textbooks, for the district court to address in the first instance."

Id. at 13.

> "Whether a pH value can be measured precisely—and to what degree—is a question of fact which we leave for the district court to determine in the first instance."

Id. at 9 n.2.

As the Federal Circuit acknowledged, these factual determinations are reserved to the district court, as finder of fact, subject to review only for clear error. *Id.* at 6 (citing *MasterMine Software, Inc. v. Microsoft Corp.*, 874 F.3d 1307, 1310 (Fed. Cir. 2017)) ("In cases where the district court reviews extrinsic evidence to resolve factual disputes, such as the background science or the meaning of a term to a skilled artisan, … those determinations must be reviewed under the clear error standard.").

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[7] The Federal Circuit's citation to page 339 is based on the pagination of the PDF format of the document. It corresponds to the page numbered 387 within the textbook itself.

Mylan has stipulated that, under Actelion's and Judge Keeley's construction, its proposed generic product literally infringes. Dkt. 185 at 3. Actelion believes that Mylan's proposed generic product has a pH that infringes under any construction, including Mylan's incorrect proposed construction. Claim construction, however, is separate from an infringement analysis under Federal Circuit law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc) ("An infringement analysis entails two steps. The first step is determining the meaning and scope of the patent claims asserted to be infringed. The second step is comparing the properly construed claims to the device accused of infringing."). This brief is limited to the first question.

III. PATENT BACKGOUND

Actelion's claim construction briefing before Judge Keeley presented a detailed discussion of the patents. Dkts. 76, 77. The Federal Circuit made clear that the extrinsic evidence analysis is to be conducted from the standpoint of the "meaning to a person of ordinary skill in the art." *Actelion Pharms.*, slip op. at 9. The patent has an effective filing date of 2006: "[t]his patent application claims the priority of U.S. Provisional Patent Application . . . filed 2006 . . . ." '802 patent at 1:1–7. The '802 and '277 patents share a common parent application and the same specification. For the narrow purpose of this briefing, there are no material differences between these two patents.

The claims cover a composition comprising epoprostenol, arginine, and sodium hydroxide. The disputed limitation recites that the composition is "formed from a bulk solution having a pH of 13 or higher." A pH of 13 is a highly basic, as opposed to acidic, composition. The FDA was concerned that a highly basic composition would be dangerous to patients by destroying blood cells. The design, however, was extraordinary. The composition has several important characteristics, including: (1) it "is highly resistant to microorganism," '802 Pat. at 4:45; (2) "it

was surprisingly found that blood cell lysis did not occur," *id.* at 4:41–42; and (3) the active ingredient does not degrade: "stability of the present formulation is characterized by at least 90% of the original epoprostenol remaining after 24-48 hours at 15-30° C," *id.* at 4:17–19.

IV. ARGUMENT

The extrinsic evidence, including the textbooks submitted by Actelion and identified by the Federal Circuit as pertinent for evaluation on remand, confirms Actelion's construction, adopted by Judge Keeley during the original claim construction: "pH of 13" carries its plain and ordinary meaning of pH 13, subject to standard rounding principles for whole numbers (*i.e.*, 12.5 to 13.4).

A. Standard Principles of Rounding

The Federal Circuit identified as a factual question appropriate for this Court to address, "what the significant digits are for 'a pH of 13.'" *Actelion Pharms.*, slip op. at 2. Mylan answered this question in its briefing before Judge Keeley. Mylan confirmed that it does not dispute the number "13" has only two significant digits. Instead, Mylan argues that portions of the specification also include measurements that have more significant digits, and on that basis seeks to import additional digits (such as x.0 or x.00) into the claim.

> In other words, while "13" may have two significant figures, the specification shows multiple examples of three significant figures (one decimal place) and four significant figures (two decimal places).

Mylan's Responsive Claim Construction Brief (D.I. 75) at 13.

> (Mylan counsel): Thirteen, one, three, two significant figures, one and three. 13.0 is three significant figures. We saw examples in the table of 11.58, 11.66. When you have two decimal places, that would be four significant figures.

Ex. 11, Claim Construction Hearing Tr., at 65:14-19.

Extrinsic textbooks submitted by Actelion teach the standard rules of rounding to the last significant digit:

> When rounding off a number, if the digit following the required rounding off digit is 4 or less, you maintain the last reportable digit and if it is six or more you increase the last reportable digit by one. If it is a five followed by more digits except an immediate zero, increase the last reportable digit. If there is only a five with no digits following, increase reportable odd digits by one and maintain reportable even digits.

Ex. 3, Kerr at 9.

Thus, based on canonical math, reported values from 12.5 to 13.4 round to 13. Another extrinsic textbook submitted by Actelion, Kerr, further confirms that this same rule is used in an exponential. It gives the example that, for $10^{3.633}$, "the order of magnitude is 10^{4}." *Id.* at 2.

Consistent with the standard math set forth in these textbooks, a person of skill understands that reported pH values from 12.5-13.4 (corresponding to $10^{-12.5} - 10^{-13.4}$) slot into the whole number score of pH 13 (corresponding to 10^{-13})[8]; *see also id.* at 1 ("The order of magnitude of a number is the power of ten closest to that number.").

These standard rounding principles have been applied by other courts, including in the context of pH. *See, e.g.*, *Vifor Fresenius Med. Care Renal Pharma Ltd. v. Teva Pharms. USA, Inc.*, 623 F. Supp. 3d 389, 416–17 (D. Del. 2022) (considering factual evidence and rejecting argument that "pH of 3" requires a "pH of 3.0"); *id.* at 417 (finding that pH values of 3.22 and 3.28 were both "at a pH of 3," consistent with "mathematical rounding principles"); *Allergan, Inc. v. Teva Pharms. USA, Inc.*, No. 2:15-CV-1455-WCB, 2016 WL 7210837, at *17 (E.D. Tex. Dec. 13, 2016) ("The patentees chose the number of significant figures to use in the claimed percentages. Those numbers would naturally be assumed to include percentages that would round up or down to 0.05% and 1.25%—that is, roughly 0.045% to 0.054% for cyclosporin A and 1.245% to 1.254% for castor

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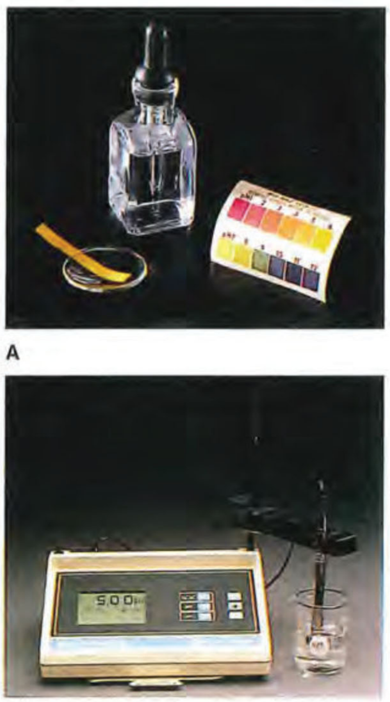
[8] pH values represent the negative logarithm of the hydrogen ion concentration in a solution. Thus, pH 12.5 is (- log$10^{-12.5}$), pH 13.4 is (- log$10^{-13.4}$)), and pH of 13 is (- log10^{-13}), with $10^{-12.5}$, $10^{-13.4}$, and 10^{-13} representing hydrogen ion concentrations in M (mol/L).

oil"); *Noven Pharms., Inc. v. Actavis Lab'ys UT, Inc.*, No. CV 15-249-LPS, 2016 WL 3625541, at *3–5 (D. Del. July 5, 2016) (rejecting defendant's attempt to construe "15 mg/cm^2" as 15.0 mg/cm^2," and noting that rounding would include +/- .5). As discussed below, additional extrinsic evidence further compels this conclusion here.

B. Measurement And Reporting of pH in 2006

The Federal Circuit asked the Court to consider "[w]hether a pH value can be measured precisely—and to what degree—[] a question of fact which we leave for the district court to determine in the first instance." *Actelion Pharms.*, slip op. at 9 n.2. The extrinsic record shows that there are a wide variety of mechanisms that measure or report pH with differing levels of precision. The images at left from the Silberberg publication cited by the Federal Circuit are two examples, both of which are indirect methods of reporting the magnitude of hydrogen ions in a solution. Ex. 4, Martin S. Silberberg, CHEMISTRY: THE MOLECULAR NATURE OF MATTER AND CHANGE, at 777 (4th ed. 2006) ("Silberberg"). The first involves the use of pH paper (Image A) which matches color to the 0-14 one step pH scale. The second involves the use of an electrode and current to indirectly estimate the magnitude of hydrogen ions (Image B), which in this example can read out two additional digits. The Kessel text cited by the Federal Circuit also makes clear that there are differing methods of measurement and reporting with differing levels of precision, which



A

B

Figure 18.7 Methods for measuring the pH of an aqueous solution. A, A few drops of the solution are placed on a strip of pH paper, and the color is compared with the color chart. **B,** The electrodes of a pH meter immersed in the test solution measure [H_3O^+]. (In this instrument, the two electrodes are housed in one probe.)

disproves Mylan's argument that pH is an "exact" number: "[t]here are several different ways of measuring the pH of a solution, some more precise than others." Ex. 2, Kessel at 543.

In past briefing, Mylan argued that the meter in Image B and two similar pictures show that "pH meters at the time of the invention would have been able to read a pH of 13.00[.]" Mylan Responsive Claim Construction Brief (Dkt. 75) at 21. But the fact that some meters could report pH at 13.00 does not help Mylan's argument; rather, it shows why the argument cannot be right. The patents do not refer to readings of 13.00. The specification primarily describes pH values at the whole number level ("pH of 13"). It also describes a handful of specific experiments on substances reported to one decimal place, while primarily focusing on whole number values. *See, e.g.*, '802 patent at 5:41–43 ("The pH of the bulk solution is preferably adjusted to . . . 13"), 11:54–56 ("the stability of epoprostenol is better at pH 13 compared to lower pH samples"), 11:60 ("with the pH of bulk solution adjusted to 13"), 9:50–53 ("the pH of the solution containing epoprostenol and arginine was adjusted to 13.0 with sodium hydroxide"), Tbls. 10-18.

Neither the fact that some pH meters exist that read out to the hundredths place (x.00), nor that some of the solutions used in experiments in the patents were reported to the tenths place (x.0), somehow engraft that level of precision into the claims. To the contrary, they further evidence that the patentee's decision to claim pH instead using the whole number (13) was intentional. The extrinsic evidence confirms that the difference between a whole number, one decimal place, and two decimal places was fully understood by a person of skill, and that an artisan would recognize the claim language "pH of 13" as adopting a whole number approach.

The testing evidence also conclusively disproves Mylan's primary argument that "pH of 13" means "exactly 13." None of the methods described in the extrinsic evidence purport to count individual hydrogen ions, nor would they be capable of obtaining anything close to an "exact"

count. For example, there are more than 10^{25} molecules of water per liter,[9] meaning that a liter of aqueous solution has something on the order of 10,000,000,000,000,000,000,000,000 molecules. The purpose of a pH measurement is not to get to anything close to that level of granularity.

The applicant's choice of "pH of 13," rather than requiring specific decimal digits, makes particular sense for other reasons illuminated by the extrinsic evidence. For context, in the preferred embodiment, the solution with pH "greater than 13" is created by "adjusting the pH of the bulk solution" by adding "**sodium hydroxide**." '802 patent at 5:23–30, 35–43 (emphasis added). At the time of the invention, sodium hydroxide was sold commercially by multiple suppliers with pH reported as the whole number "pH 13" or "pH 13-14",[10] even though, as discussed above, various testing methods and apparatuses, such as pH meters, had the ability to report additional granularity.

DENSITY/SPECIFIC GRAVITY (g/ml):	213	Temperature (°F): 68
BULK DENSITY:	133 lb/cu.ft; 2131 kg/m3	
WATER SOLUBILITY:	Soluble	
VAPOR DENSITY (air=1):	N/A	
VAPOR PRESSURE:	42 mmHg	Temperature (°F): 1832
pH-VALUE, DILUTE SOLUTION:	13	Concentration (%M): 1%

IV. PHYSICAL DATA

APPEARANCE: Clear, viscous liquid
FREEZING POINT: -26 Deg.C (-15 Deg.F) 20% solution
-17 Deg.C (1.4 Deg.F) 25% solution
2 Deg.C (36 Deg.F) 30% solution
BOILING POINT: No Data
DECOMPOSITION TEMPERATURE: Stable at normal temperatures
SPECIFIC GRAVITY: No Data
DENSITY @ 20 Deg.C: 1.22 g/cc (10.16 lbs./gal.) 20%
1.27 g/cc (10.62 lbs./gal.) 25%
1.33 g/cc (11.07 lbs./gal.) 30%
pH @ 25 DEG.C: 13 (0.5% solution)

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[9] *See* Actelion Op. Brief (Dkt. 76) at 14 n.6.

[10] *See, e.g.*, Ex. 6, Philip A. Hunt Chemical Corporation, *Sodium Hydroxide Caustic Soda 30%*, at 1 (1996) (pH 13); Ex. 5, TETRA Technologies, Inc., *Caustic Soda*, at 3 (2001) (pH 13); Ex. 7, Fischer Scientific, *Sodium Hydroxide 1N*, at 4 (2005) (pH 13-14).

Color:	colorless
Odor:	practically odorless
pH:	13-14
Vapor Pressure:	Not available
Vapor Density:	>1.0
Evaporation Rate:	Not available
Viscosity:	Not available
Boiling Point:	> 100 deg C (> 212.00°F)
Freezing/Melting Point:	> 0 deg C (> 32.00°F)
Decomposition Temperature:	Not available
Solubility in water:	Slightly soluble
Specific Gravity/Density:	>1.0
Molecular Formula:	Solution
Molecular Weight:	0

Similarly, the FDA-approved label for Actelion's Veletri® (the inventive product protected by the patents) reports whole numbers, even though the technical capability to report additional digits exists:

> The reconstituted solution of VELETRI has a pH ranging from 11 to 13 and is increasingly unstable at a lower pH.

Ex. 8 at Appx0236.

This extrinsic evidence further emphasizes that a POSA understood the difference between claiming a whole number on the pH scale (13), rather than narrowly limiting it with additional decimal digits such as 13.0 or 13.00. This goes directly to the Federal Circuit's instruction to consider the "meaning to a person of ordinary skill in the art as regards precision of measurement, significant digits, or rounding." *Actelion Pharms.*, slip op. at 9.

C. pH Is A Simplified Representation Of The Degree To Which A Solution Is Basic Or Acidic

The pH scale ranges from 0-14, with one-unit steps in between. These steps represent the comparative degree to which a solution is basic or acidic. The more acidic a solution is, the more hydrogen [H_3O^+] ions[11] are present. This is shown in the scale as depicted in the Mustoe textbook cited by the Federal Circuit:

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[11] Hydrogen ions also may be referred to as "hydronium" ions or "H_3O^+". Ex. 1, Mustoe at 386.

Table 10.7 Understanding pH

Range of acidity and basicity	$[H_3O^+]$ (mol/L)	Exponential notation (mol/L)	log	pH ($-\log [H_3O^+]$)
strong acid	1	1×10^{0}	0	0
	0.1	1×10^{-1}	−1	1
	0.01	1×10^{-2}	−2	2
	0.001	1×10^{-3}	−3	3
	0.000 1	1×10^{-4}	−4	4
	0.000 01	1×10^{-5}	−5	5
	0.000 001	1×10^{-6}	−6	6
neutral $[H^+] = [OH^-] = 1.0 \times 10^{-7}$	0.000 000 1	1×10^{-7}	−7	7
	0.000 000 01	1×10^{-8}	−8	8
	0.000 000 001	1×10^{-9}	−9	9
	0.000 000 000 1	1×10^{-10}	−10	10
	0.000 000 000 01	1×10^{-11}	−11	11
	0.000 000 000 001	1×10^{-12}	−12	12
	0.000 000 000 000 1	1×10^{-13}	−13	13
strong base	0.000 000 000 000 01	1×10^{-14}	−14	14

Hydrogen ion concentration

pH whole number scale

When a measurement is taken of a solution that has increased precision to the 1/10th place (x.0) (for example), a person of skill knows exactly where to place it on the whole number pH scale recited in the claim:

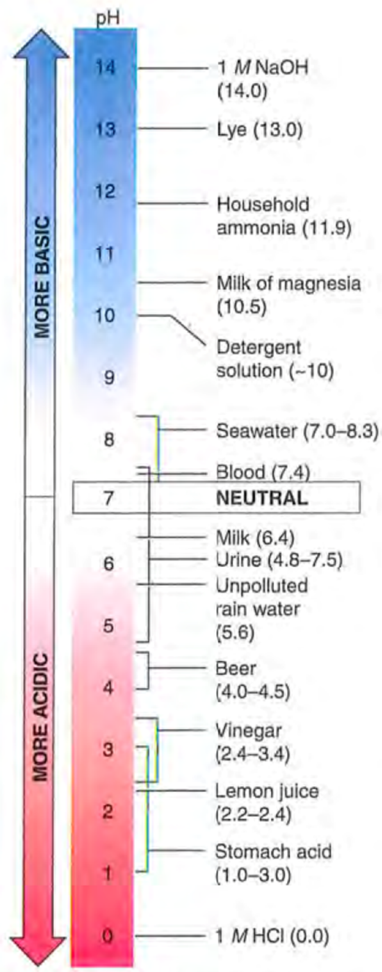
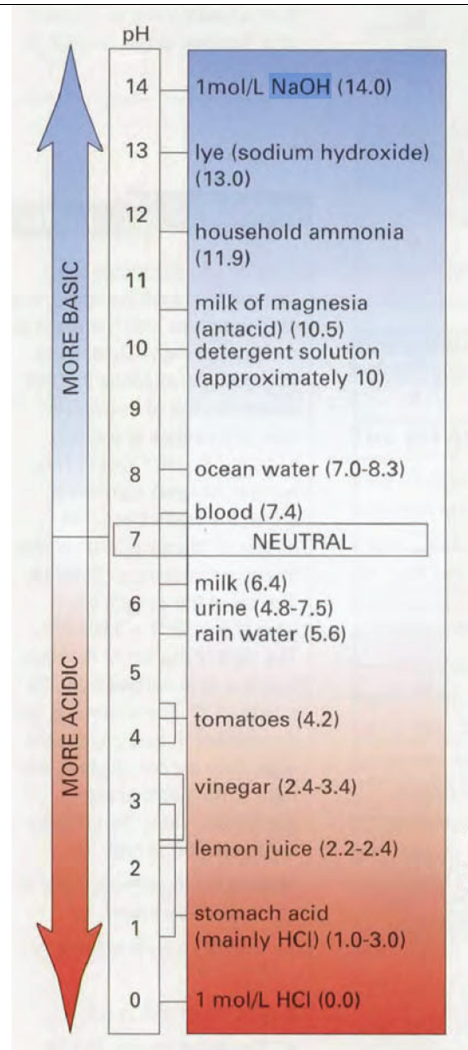


Figure 18.5 The pH values of some familiar aqueous solutions.



Ex. 4, Silberberg at 775; Ex. 1, Mustoe at 388.

Consistent with the extrinsic evidence, the claims are drafted to encompass the various different levels of precision with which pH can be measured and reported. As the Kessel textbook states, "[t]here are several different ways of measuring the pH of a solution, some more precise than others." Ex. 2, Kessel at 543. It is for this reason, the Kessel textbook explains, that the pH scale does not reflect a "unit" of measurement, like 10 millimeters or 100 kilograms, but instead a magnitude:

> "Because of the tremendous range of hydrogen ion and hydroxide ion concentrations, scientists rely on a simple system for communicating concentrations.

> This system, called the pH scale, was developed in 1909 by Danish chemist Soren Sorenson. Expressed as a numerical value without units, the pH of a solution is the negative of the logarithm to the base ten of the hydrogen ion concentration."

Id. at 540.

The Federal Circuit recognized this point that the pH system is a scaled range, not a unit of measurement, stating:

> "[T]he claims do not recite just any measurement of 13 or higher; rather they are directed to a pH of 13 or higher. Thus, the district court should consider whether a pH of 13 carries any meaning to a person of ordinary skill in the art as regards precision of measurement, significant digits, or rounding."

Actelion Pharms., slip op. at 9. The extrinsic evidence, including the specific publications that Actelion submitted and the Federal Circuit identified, answer this question. As the Mustoe textbook explains, "the 'p' in pH stands for the word 'power.' The power referred to is exponential power: the power of 10." Ex. 1, Mustoe at 386; *see also* Ex. 2, Kessel at 541 ("the definition of pH establishes an inverse relationship between the magnitude of the hydrogen ion concentration and the magnitude of the pH value.").

The purpose of this power of ten representation is to show ***relative*** differences in magnitude, making it much easier to work with, for example, "very small values, such as 0.000 000 000 000 01." Ex. 1, Mustoe at 386. This addresses a consideration not unique to chemistry: "Often when dealing with very big or very small numbers, scientists are more concerned with the order of magnitude of a measurement rather than the precise value." Ex. 3, Kerr at 1. Simply put, the pH scale is inherently an indirect comparative scale, not a precise unit of measurement like a millimeter or a kilogram.

D. pH Expressed As A Whole Number Defines An Order Of Magnitude That is Rounded

When pH is expressed using a whole number, as in the claims ("pH of 13"), that represents the order of magnitude. The "Understanding pH" table from the Mustoe textbook, below, shows the orders of magnitude associated with pH values of 0-14.

Table 10.7 Understanding pH

Range of acidity and basicity	$[H_3O^+]$ (mol/L)	Exponential notation (mol/L)	log	pH (-log $[H_3O^+]$)
strong acid	1	1×10^{0}	0	0
	0.1	1×10^{-1}	−1	1
	0.01	1×10^{-2}	−2	2
	0.001	1×10^{-3}	−3	3
	0.000 1	1×10^{-4}	−4	4
	0.000 01	1×10^{-5}	−5	5
	0.000 001	1×10^{-6}	−6	6
neutral $[H^+] = [OH^-]$ $= 1.0 \times 10^{-7}$	0.000 000 1	1×10^{-7}	−7	7
	0.000 000 01	1×10^{-8}	−8	8
	0.000 000 001	1×10^{-9}	−9	9
	0.000 000 000 1	1×10^{-10}	−10	10
	0.000 000 000 01	1×10^{-11}	−11	11
	0.000 000 000 001	1×10^{-12}	−12	12
	0.000 000 000 000 1	1×10^{-13}	−13	13
strong base	0.000 000 000 000 01	1×10^{-14}	−14	14

Order of magnitude

pH whole number scale

For pH, the whole number "13" communicates that the solution has a hydrogen ion concentration on the order of magnitude of 10^{-13}. Ex. 1, Mustoe at 387. That solution is a strong base. For example, as shown above, it has on the order of 1,000,000 times fewer hydrogen ions as compared to a neutral solution (pH 7, 10^{-7}). Because the scale is based on powers of ten, the solution of pH 13 has on the order of 10 times fewer hydrogen ions as compared to a solution of pH 12.

The fact that the pH scale is not “units of measurement” but instead orders of magnitude further leads a person of ordinary skill to understand that all reported pH values from 12.5-13.4 ((- $\log 10^{-12.5}$) – (- $\log 10^{-13.4}$)) are within “pH of 13” (- $\log 10^{-13}$). This is because standard textbooks explain that the exponential portion is rounded to the nearest order of magnitude, giving the example that, for $10^{3.633}$, “the order of magnitude is 10^4.” Ex. 3, Kerr at 2.

The Silberberg textbook presented by Actelion provides an example of calculating pH where relatively precise data on the comparative amount of hydrogen ion is available (the red box, listing 5.4). This, in turn allows a calculation that includes two decimal places (the green box, listing 3.27).

$$\mathrm{pH} = -\log\,[\mathrm{H_3O^+}] = (-1)(\log \boxed{5.4} + \log\, 10^{-4}) = \boxed{3.27}$$

Ex. 4 at 775. On the exact same page, however, the textbook instructs the reader how to map to the pH **scale**, employing **whole numbers** (in the example, 12) from the pH scale, even though experimentally it is possible to measure with more digits:

What is the pH of 10^{-12} M $\mathrm{H_3O^+}$ solution?

$$\mathrm{pH} = -\log\,[\mathrm{H_3O^+}] = -\log\, 10^{-12} = (-1)(-12) = \boxed{12}$$

Id.

Indeed, the Federal Circuit noted that multiple textbooks presented by Actelion confirm that the way to identify “significant digits in a pH” is by counting the number of “digits to the right of the decimal point.” *Actelion Pharms.*, slip op. at 5 (quoting Mustoe at 339); *see also* Ex. 4,

Silberberg at 775 ("it is a logarithm, so the number of significant figures in the concentration equals the number of digits *to the right of the decimal point in the logarithm*[.]") (emphasis in original); Ex. 2, Kessel at 541 ("the digits in the exponent of the given hydrogen ion concentration…have no connection with the certainty of the value.").

This evidence is ultimately dispositive because, in the claims of the patents-in-suit, there are no digits to the right of the decimal point. There is, in fact, no decimal point. For the purposes of the claims, the applicant used the nomenclature "pH of 13," intentionally using a whole number as opposed to limiting the claims to, for example, 13.0 or 13.00. Because the claim language "pH of 13" does not state digits to the right of a decimal point, no additional significant digits are read into the claims. The only significant digits present in the claim are the two digits in the whole number "13" itself which, as discussed above, is subject to ordinary rounding (12.5-13.4).

And, as discussed above, it was well understood at the time of the patent that using a whole number meant the order of magnitude of hydrogen ion concentration associated with the pH level (here, 10^{-13}). Exponentials are rounded to the nearest order of magnitude, as discussed above. *See* Ex. 3, Kerr at 2 (for $10^{3.633}$, "the order of magnitude is 10^4").

The extrinsic evidence shows that whether a particular solution is reported using the whole number color-matching apparatus showing in Silberberg, the particular pH meter shown in the Silberberg text which reports out two decimal points, or any other method, the result is the same. If it produces a number that rounds to 13 (12.5 to 13.4), it is order of magnitude 10^{-13}, and therefore "pH of 13" as understood by a person of ordinary skill.

V. PROPOSED FINDINGS OF FACT BASED ON THE EXTRINSIC EVIDENCE

In light of the extrinsic evidence in the record, Actelion respectfully requests that the Court make the following findings of facts as to the understanding of a person of ordinary skill in the art as of the 2006 filing date of the application:

1. There were several different ways of reporting pH of a solution, some more precise than others.
2. Options for reporting pH of a solution included various testing methods and apparatuses that reported whole numbers only, as well as mechanisms that reported one or two decimal places.
3. There is no practical method of directly or precisely calculating the number of hydrogen ions in a solution that make it more basic or acidic.
4. The pH scale is a whole number scale with single number steps between 0-14. It was designed to be a "simple" scale without units of measurements, representing the degree to which a solution is basic or acidic.
5. pH 13 on the pH scale reflects a hydrogen ion concentration of 10^{-13}.
6. Because the claim language "pH of 13" does not state digits to the right of a decimal point, the only significant digits present in the claim are the two digits in the whole number "13."
7. Under standard mathematical rounding, values reported as 12.5 to 13.4 round to the whole number 13.
8. Textbooks confirm that, for orders of magnitude, exponentials reported with digits to the right of a decimal point are similarly rounded (for example, for $10^{3.633}$, "the order of magnitude is 10^4").

9. A person of ordinary skill in the art understands that pH reported at 12.5 (corresponding to $10^{-12.5}$) through 13.4 (corresponding to $10^{-13.4}$) would be rounded and placed on the pH scale at location pH 13.

10. The patentee's selection of a whole number pH value of 13, without limiting it to 13.0 or 13.00, also is consistent with the fact that, at the time of the invention, sodium hydroxide (the base identified in the preferred embodiment) was sold commercially as "pH 13" or "pH 13-14."

11. The extrinsic evidence confirms that a "pH of 13" carries its plain and ordinary meaning of pH 13, subject to standard rounding principles for whole numbers (*i.e.*, 12.5 to 13.4).

Respectfully submitted,

By: */s/ Chad L. Taylor*

Frank E. Simmerman Jr. (WVSB# 3403)
Chad L. Taylor (WVSB# 10564)
Frank E. Simmerman, III (WVSB# 11589)
SIMMERMAN LAW OFFICE, PLLC
254 East Main Street
Clarksburg, West Virginia 26301
fes@simmermanlaw.com
clt@simmermanlaw.com
trey@simmermanlaw.com
(304) 623-4900 (Telephone)
(304) 623-4906 (Facsimile)

Attorneys for Plaintiff
Actelion Pharmaceuticals Ltd

Of Counsel:

Jason G. Sheasby
Lisa Glasser
IRELL & MANELLA LLP
1800 Avenue of the Stars,
Suite 900
Los Angeles, CA 90067
jsheasby@irell.com
lglasser@irell.com
(310) 277-1010 (Telephone)

Bruce M. Wexler
Preston K. Ratliff II
Aaron P. Selikson
Christopher P. Hill
Mark Russell Sperling
PAUL HASTINGS LLP
200 Park A venue
New York, NY 10166
(212) 318-6000

(310) 203-7199 (Facsimile)
Pro Hac Vice Pending

Attorneys for Plaintiff
Actelion Pharmaceuticals Ltd

Attorneys for Plaintiff
Actelion Pharmaceuticals Ltd

UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

Clarksburg

ACTELION PHARMACEUTICALS LTD, Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	**Civil Action No. 1:20-cv-110** **Honorable John Preston Bailey** **CERTIFICATE OF SERVICE**

I, Chad L. Taylor, Esq., counsel for Plaintiff, do hereby certify that on the 21st day of November, 2023, the foregoing **ACTELION'S BRIEF REGARDING EXTRINSIC EVIDENCE SUPPORTING THE COURT'S CLAIM CONSTRUCTION** was filed electronically via the Court's CM/ECF system which will send notice of the same to counsel of record.

By: *<u>/s/Chad L. Taylor</u>*______________

Chad L. Taylor (WVSB# 10564)
clt@simmermanlaw.com
SIMMERMAN LAW OFFICE, PLLC
254 East Main Street
Clarksburg, West Virginia 26301
(304) 623-4900 (Telephone)
(304) 623-4906 (FACSIMILE)